Direction and Utility of Growth Biology Research

Harry J. Mersmann*

The long-range problem of biologists working with animals raised as sources of meat is to efficiently produce high quality, palatable protein for human consumption. Since the palatability and quality of meat is usually acceptable, a major problem is to maximize production efficiency. This will be accomplished primarily by minimization of resource input (animal feed, energy, labor, facilities, etc.) coupled with simultaneous maximization of product output (lean or muscle mass) and minimization of waste (excess fat mass).

It has always been important to the producer and ultimately to the consumer to efficiently produce a food commodity. However, as the U.S. economy has changed markedly in the last decade, there has been and will continue to be increased pressure to maximize efficiencies. The higher cost of fossil fuels impinges on animal production both directly through the use for heat, light and machinery in intensive animal production facilities and indirectly in the production of animal feeds. A major consideration in the production of meat as a protein source is the impact that competition for grain as a direct human food source in most of the world will have on the production of meat protein (Barr, 1981). Regardless of the ultimate solution to grain distribution throughout the world, it appears that competition with livestock feeding will remain and consequently production efficiency will become increasingly important (Ward, 1980). In addition there may be competition between grain use for animal production and for synthesis of fuel (Lipinsky, 1978).

The topic of this discussion can be described as growth biology and will address the proliferation and differentiation of muscle and adipose tissue at the cellular level with particular emphasis on meat producing animals. Many aspects of research needs in growth biology of muscle and adipose have been discussed recently (Intersociety, 1980).

Current Knowledge. Although many animal scientists are interested in animal growth and in muscle and fat production, few address the questions at the cellular level. Animal biologists currently use classical animal breeding techniques for long term (genetic) improvement and nutritional approaches for immediate improvement in animal production efficiency and alteration of body composition. Progress has been made over the past years by applying these techniques through experimental designs that essentially feed and weigh animals and assess performance using simple devices to measure linear and mass units. Knowledge of the underlying cellular events responsible for the observed changes is critically limited. Consequently, although the end result has been a desired effect, it is masked in the complexities of all other aspects of the animal's life.

In the past there has been little basic animal biology in the agricultural sector. Specifically, the area of growth biology has not been supported at a substantial level or on a continuous basis. For example, considerable information regarding metabolism of adipose tissue in meat producing animals was accrued in the early and mid 1970's (Allen et al., 1976); however, by the latter portion of the 1970's and into the 1980's the level and sources of support (mostly not agricultural) diminished so that at the present time only a few investigators have ongoing research efforts in the area. Some progress has been made in understanding growth biology in meat producing animals; however, we have only impinged on the surface of the real questions about regulation of muscle and adipose tissue growth. The limited knowledge that we have from past research on meat animals, coupled with that gleaned from biomedical research, provides a foundation from which critical questions may be formulated pertaining to meat animal muscle and adipose tissue growth biology.

Future Knowledge. General patterns of growth of adipose and muscle tissue may be discerned from biomedical models; however, the species differences in metabolic processes preclude extrapolation of these general patterns to the level of knowledge needed to ultimately manipulate the meat animal for maximal efficiency of lean meat production. Technologies used in basic biology and biomedical research need to be introduced so that questions pertaining to growth biology in meat producing animals may be answered. Techniques common to cell biology, biochemistry, biochemical genetics, immunology, etc. must be applied to *in vitro* cell-free systems to understand the regulation and control of biosynthetic and degradative metabolic pathways involved in protein and fat accretion. These techniques must be extended to the cellular level and ultimately to the whole animal. Cell culture systems (both primary and secondary) must be employed to fathom the regulatory processes pertaining to cell proliferation and differentiation of muscle and adipose tissues. For example, the

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*H. J. Mersmann, USDA, SE, ARS, Roman L. Hruska U.S. Meat Animal Research Center, P.O. Box 166, Clay Center, NE 68933

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extreme complexity of the patterns of secretion of the multitudinous endocrine factors currently being observed in intact animals (Morrison et al., 1981) cannot become meaningful or allow manipulation of the animal to maximize protein production until endocrine effects are discerned at the cellular level.

Research Approaches

A. Hyperplasia. The mass of a particular tissue is ultimately limited by the number of cells present, since the maximal cell volume appears to be fixed for a given cell type. One goal of growth biology research in meat animals is to control hyperplasia (cell replication or division) so that muscle cell number is increased leading to greater muscle mass and adipose tissue cell number is decreased leading to lesser adipose tissue mass. In both tissues the increase in cell number appears to be predominant in fetal or neonatal stages of growth. It seems to occur in undifferentiated muscle and adipose tissue cells and not in cells sufficiently differentiated to display the attributes of the mature cell type. For example, differentiation by fusion of the myoblast or dividing muscle precursor cell to produce the multinucleated myotube, followed by synthesis of contractile proteins, produces a cell that apparently no longer divides. Although less is known about the adipose tissue precursor cell, the available evidence suggests that differentiated adipose tissue cells also do not divide.

The regulation of hyperplasia is essentially undefined in both muscle and adipose tissue. Hyperplasia is ultimately a genetically regulated phenomena since the primary event is replication of the genetic material. Although little is known about genetic regulation in either of the tissues of interest, it appears that endocrine factors can regulate genetic expression. For example, a number of somatotropic hormones secreted by the central nervous system, including growth hormone and prolactin do not appear to act directly on muscle cells (in culture systems), rather, they seem to stimulate other tissues to produce growth factors that are secreted into the blood stream and control hyperplasia. A variety of growth stimulating factors (*e.g.*, fibroblast growth factor, multiplication stimulating factor, various somatomedins, etc.) increase hyperplasia in cell culture models, including cells derived from muscle (Paul, et al., 1978; Gospodarowicz, 1979; Ewton and Florini, 1980). There are probably specific receptors on the cell surface for binding of the growth factors with control of hyperplasia a manifestation of the formation of the factor-receptor complex, possibly after internalization into the cell (Adamson and Rees, 1981).

There is limited information regarding control of hyperplasia in adipose tissue. Cells have been isolated from adipose tissue that proliferate in culture and eventually differentiate to adipocytes (Van et al., 1976; Bjorntorp et al., 1980), as well as cell culture lines derived from fibroblasts that differentiate to adipocyte-like cells under specific culture conditions (Green and Kehinde, 1975). In the former cell type, an estrogen and several pituitary peptides enhance proliferation of precursor cells (Roncari, 1981). Most studies on adipose cell culture systems concern the control of differentiation to mature adipocytes.

In mature muscle, satellite cells (a cell type adjacent to the myofibril or muscle cell) divide. Satellite cells can fuse with myofibrils and thus may represent a specialized type of hyperplasia in the mature muscle (Allen et al., 1979). The satellite cell also has been implicated in muscle regeneration processes wherein hyperplasia is increased. Recently there is evidence for cell division in mature adipose tissue although the functional significance is not known (Klyde and Hirsch, 1979).

There is little knowledge pertaining to the control of hyperplasia by intracellular nutrition. The process of hyperplasia is certainly at least partially regulated by the qualitative and quantitative mix of intracellular substrates (nutrients) since there is great demand for energy as well as nucleic acid and protein precursors during cell division. Knowledge of the regulation of hyperplasia by intercellular interactions is limited also in muscle and adipose tissue. Neither muscle nor adipose precursor cell types differentiate in culture until there is considerable contact between growing cells. Apparently, there are necessary membrane interactions between cells, exchange of materials between cells or production and secretion to the medium of factors required for the initiation of differentiation.

The major questions to be answered regarding muscle and adipose tissue hyperplasia are:

1. What controls hyperplasia in the early stages of growth?
2. What is the trigger to arrest cell division upon differentiation or what triggers differentiation?
3. Does muscle or adipose tissue continue hyperplasia after the neonatal stages of development?

B. Hypertrophy. Most hypertrophy, or increase in cell size, occurs in postnatal and growing stages of animal development. Since the cell number in muscle and adipose tissue appears relatively fixed (the possibility for continued hyperplasia in growing animals must be kept open), the extent of hypertrophy is a major determinant of the tissue mass. The goal of growth biology research is to develop technologies to decrease adipose tissue cell size and increase muscle cell size, thus increasing the yield of lean or protein mass.

The cell is in a dynamic state; there are multiple biosynthetic processes that produce the variety of cellular entities and organelles coupled with concomitant degradative processes. Hypertrophy or the accretion of mass (primarily contractile proteins in muscle cells and triglyceride in adipose tissue cells) is the net result of both synthetic and degradative pathways and may be controlled by either or some combination of both.

The biochemical pathways involved in many aspects of the synthetic processes are reasonably well known for both protein and fat. In fact, there is considerable information regarding the pathways for synthesis of fat in ruminant and nonruminant adipose tissue from meat producing species (Allen et al., 1976; Vernon, 1980; Numa and Yamashita, 1974). Although much is known about the pathways for protein synthesis, details of the protein synthetic pathways in muscle from meat producing animals are lacking (Young, 1975; Pain and Clemens, 1980). The pathways for lipid degradation are modestly understood in ruminant and nonruminant adipose tissue (Allen et al., 1976; Vernon, 1980) but the pathways and enzymes involved in protein degradation in skeletal muscle have not been delineated in any species (Bird et al, 1980; Goldberg et al., 1980; Laurent and Millward, 1980).

Details of all of these metabolic pathways in meat producing animals are unknown. For example, the physiological substrates for lipid synthesis or the metabolic controls for the

regulation and integration of the several pathways for fat synthesis are poorly understood. Although there are multiple hormonal and metabolic regulators for *in vitro* degradative processes in adipose tissue, the *in vivo* effectors for the breakdown of adipose tissue are not known. The control of protein synthesis in muscle is likewise little understood from the perspective of regulatory events and, as mentioned, the degradative pathways are not understood well enough to seriously discuss regulation.

Many sex, growth and metabolic hormones influence synthesis and degradation of protein and fat in *in vitro* systems and apparently sometimes *in vivo*. Consequently, it seems obvious that endocrine factors are important in the control of hypertrophy in both muscle and adipose tissue. However, details of such control are lacking and especially are not available for meat producing animals. Likewise there is little information regarding the role of cellular nutrition in the regulation of hypertrophy. Regardless, the pathways of interest must be at least partially controlled by substrate and product levels in the cell.

As information at the cellular level is accrued, it might be extended to the whole animal and initial progress toward manipulation of protein or fat mass assessed by measurement of synthesis or degradation. Techniques are available to measure whole body protein synthesis (Buckley and Marquardt, 1981; Garlick, 1980). The cost of such experiments, as well as similar experiments to measure fat synthesis, would limit their utility in large animals. Muscle protein degradation has been measured in the whole animal (Garlick, 1980; Harris and Milne, 1981), whereas whole animal fat degradation is more problematical.

The major questions to be answered in regard to hypertrophy of muscle and adipose tissue are:

1. What controls the accretion of fat in adipose tissue and protein in muscle? Are these endocrine controls? Does nutrition (gross or cellular) exert direct effects on hypertrophy?
2. Can protein deposition in muscle be accelerated and/or fat deposition in adipose tissue be decelerated? Can it be accomplished first at the *in vitro* level and then extended to the *in vivo* level?

C. Partition of Nutrients. In growing animals the accretion of muscle and fat mass is nonlinear. Muscle mass increases more rapidly than fat mass in the early stages of postnatal growth, whereas the reverse is true in the latter stages of growth. (Forrest et al., 1975; Lister, 1980; Webster, 1980; Berg and Butterfield, 1976). The energetic and protein components of the diet must be distributed preferentially to these respective tissues depending on the stage of growth. The controls or regulatory phenomena that allow this differential distribution of nutrients to first one tissue and then another are not understood. These might be genetic, endocrine, nutritional or intracellular in nature. It should be noted that the controls for cell hyperplasia and/or hypertrophy may ultimately regulate the partitioning of nutrients (or control of nutrient partition may well control cell hyperplasia and hypertrophy).

Sex hormones have major effects on the growth of muscle and fat tissues in most mammalian species, *e.g.*, bulls contain more muscle and less fat than heifers at about 400 kg body weight (Berg and Butterfield, 1976). There are many variations on this theme but in several species the carcass composition can be manipulated by appropriate use of anabolic steroids, *i.e.*, usually either male or female sex hormones or their synthetic analogs (Young and Pluskal, 1977; VanderWal, 1975; Trenkle, 1975). The mechanism of action of the sex hormones on differential tissue growth is not well understood. The effects may be on the tissue itself (control of synthetic or degradative pathways or of hyperplasia of muscle or adipose tissue) on the differential partition of energy and/or amino acids to the tissue or on the control of feed intake; the observed response may be different in various species.

The growth stimulating hormones secreted by the central nervous system and pituitary coupled with the many peripheral growth-promoting factors are probably also involved in the regulation of lean and fat mass production. As numerous peripheral growth factors are discovered and patterns of secretion of centrally produced hormones are discerned as exceedingly complex (Morrison et al., 1981), the site and mode of action of hormones as well as interactions between hormones becomes even more confusing (Lister, 1980). Hormones, such as insulin, glucagon, glucocorticoids and catecholamines, that control metabolic activities undoubtedly have major effects on nutrient partition. In many cases definitive information is lacking regarding their activity in meat producing animals. As an example, recent experiments indicate that insulin has minimal effects if any on the control of bovine adipose tissue lipogenesis (Prior and Smith, 1982), a result totally unpredicted from previous work with other species. The interaction of sex and growth hormones with the metabolic endocrine substances essentially has not been explored.

The critical questions in the area of nutrient partition are:

1. What are the endocrine controls? Can they be manipulated in the whole animal?
2. Is nutrient partition simply a reflection of chronological control of muscle and fat hypertrophy (and/or hyperplasia)?
3. Are there changes in the muscle or fat cell that dictate specific nutrient entry and thus control hypertrophy?

Benefits. The understanding of regulation of muscle and adipose tissue hyperplasia and hypertrophy and of nutrient partition between the two tissues as it pertains to meat-producing animals is a major basic multidisciplinary research endeavor. These growth biology research efforts require a commitment for adequate and continued support for an estimated 10 or more years. The research is high risk in nature in that the outcome is elusive and the exact technological gains not readily discernible at the present time. Since the research directions are so diverse (nutrient partition both intracellularly and in the whole animal, central and/or peripheral endocrine control, prenatal or postnatal manipulation, etc.) it is not possible to present a single scenario. However, it can be predicted that as research programs progress, knowledge of these complex biological regulatory phenomena will be applied to manipulation of animal growth.

Knowledge of the underlying regulatory events and their effect on the efficient production of meat protein would allow direct application of animal breeding principles to engineer a metabolic step or pathway or the proliferation or differentiation of a particular cell type deemed to be optimal for efficient protein production. Likewise, nutritional studies could be designed to improve the efficiency of specific cellular events controlling the processes of interest rather than through the

current assessment of gross animal weight or compositional changes.

A change in composition of animal carcasses should be cost effective since both fat and protein deposition require about equal feed input (Thorbek, 1975). (The lean mass may be estimated as about 30% or less protein (Doornenbal, 1971) so that the cost for lean growth is actually about ⅓ of that for fat growth on a weight basis.) Given a swine carcass of about 71 kg containing 47% lean and 29% fat mass (Evans, 1979) a crude estimate can be made for a 1% increase in lean mass coupled with a concomitant 1% decrease in fat mass. Assuming the lean mass is worth $1.00 per pound and the fat mass worth $.20 per pound, such a change would result in an increase of .33 kg or .74 pounds of lean mass = $.74 and a decrease of .21 kg or .45 pounds of fat mass = minus $.09; the net change in worth would be an increase of $.65 per carcass (without consideration for possible change in feed intake). A targeted change of 5 or 10% would result in a net increase in worth of $3.25 or 6.50, respectively. Complex models generated by incorporation of feed costs, interest rates, increased or decreased overall growth rates, differential growth rates of muscle and adipose tissue and various price ranges for products would be more meaningful and bracket the range of potential outcomes. Models could also be generated for each species of interest.

Support. Industry is interested in growth biology, however, the supported research endeavors will be somewhat narrow and specialized toward a specific saleable product. It safely can be said that industrial support for growth research will be limited and its continuity unpredictable since it is directly tied to profit. The results of industrial research also are at least partially unaccessible to the public sector. There could be an exception if a particular company already is reaping considerable profit from a product in animal growth; however, the relatively small potential total market for animal growth products almost precludes extensive and long-term research support.

Growth biology research in academic institutions is limited because there are few trained personnel in the agricultural sector to engage in these endeavors. Furthermore, the few qualified people are at many institutions producing an extremely fragmented and uncoordinated effort.

Perhaps, the most direct way to progress toward the goals of growth biology is to establish a coordinated program that is consolidated at one location. Real progress in this area can be made if a critical mass of multidisciplined scientists is assembled so there is amplification and reinforcement of intellectual and facility input. It should be obvious that the general questions posed are similar for both muscle and adipose tissue. The answers may be different for the two tissues but, in a general sense, the same tools will be needed and the intellectual reinforcement between the areas will be considerable. Coordination of the efforts can only be accomplished by establishment of some formal type of project oriented team research wherein there is continual discussion of directions, progress and meaning. Coordination also mandates a designated team leader with responsibility for the attainment of the established goals.

An assembly of such a critical mass of scientists to have input into (but certainly not exhaust these complex endeavors) the major areas of research discussed might be organized as follows:

Endocrinology
- Anabolic steroids — action and mechanisms at cellular level
- Growth factors — action and mechanisms at cellular level
- Central nervous system growth factors — patterns of secretion
- Regulation of growth in primary culture

Hyperplasia and Differentiation
- Adipose tissue in culture
- Muscle tissue in culture
- Muscle satellite cells in culture

Hypertrophy
- Muscle protein synthesis
- Muscle protein degradation
- Biochemical genetics (genes for specific proteins)
- Adipose tissue synthesis
- Adipose tissue degradation

This projected research program is laboratory intensive, high cost research. In addition to the scientific personnel and the accompanying supply, facility and equipment funds, there is need for support staff (technicians, as well as graduate and postdoctoral students). Such a research program appears to meet the goals of USDA to support fundamental research areas of national scope.

The time is right to begin a real effort in animal growth biology. The tools to do the necessary research are emerging rapidly and meaningful questions can be asked and at least begun to be answered. Long-term support, coupled with the establishment of an organization with specific directions and goals, will allow real progress in this area.

Discussion

R.G. Cassens, Wisconsin: You mentioned the question of competition between animals and humans for food. I understand there is also concern for competition between animals and plants for land use. Do you have any comments about that competition?

H.J. Mersmann: I don't have any specific comments, but I feel that this competition for land use should give us incentive to maximize the efficiency of animal production. In the plant area, researchers are really making major strides at the cellular level and translating those pieces of information to practical results. The animal area of endeavor is considerably behind in that respect. Sometimes I get the impression that the people in the animal area feel that this is rather esoteric. If we don't acquire basic information about animal growth, we will be doing the same kinds of research that we are doing today ten years from now. The plant people have taken advantages of the cellular biology and are beginning to reap the benefits of it.

R.G. Kauffman, Wisconsin: Harry, I have two points to make. Number 1, you say that there is little support from agriculture for growth biology, I disagree with this point perhaps because I come from a different background. Are you saying there is a lack of financial support, moral support or from the people that are working in this area? Point number 2, is that you said we should be doing more work in looking at the role of hyperplasia and hypertrophy of muscle cells and fat

cells together rather than independently. Is this possible? How should we proceed?

H.J. Mersmann: In regard to the support question, I assume that my comments are based on the financial level and not on the interest level. There certainly has always been interest in the area of growth biology from the academic point of view. Although I have never worked at the academic level, financial support seems to have dwindled during the 70's. In regard to the question of studying both tissues together, I think that is an interesting concept because somehow in the animal they do interact. Whether the tissues interact or whether the animal interacts with the tissue is the real question. I am not sure that the tissues really do interact. I do not know of any evidence except that under necrotic conditions tissue differentiates into adipose tissue. Evidence of necrosis in damaged muscular tissue gives rise to adipose tissue. I am not aware of this occurring under normal conditions. If we were to put adipose tissue and muscle tissue in culture together, I am not sure what we would gain. On a culture plate the adipose tissue cells would aggregate in one area of the plate and the muscle tissue cells would aggregate in another area. The tissues would continue to grow assuming conditions were right for both tissues. Maybe one tissue would overgrow the other. That is probably what would happen because of the commonality of surface receptors. I don't know.

R.G. Kauffman, Wisconsin: How do we study the differential partition of nutrients if we study the tissues on an isolated basis?

H.J. Mersmann: I think we have to examine the animals at different stages of growth for that particular problem. We need to look for differential partitioning of amino acids, transport phenomena and endocrine effects on tissue. The period immediately postnatally in most species is a rapid time of growth with rapid muscle accretion. As animals approach sexual maturity, we are into stages where there is a much greater increase in fat mass. Off the top of my head, I don't know how to look at this problem in culture.

Bill Schwartz, Peter Eckrich and Company: To take this from a different perspective, I am interested in how you relate this area of growth biology to the popular area of genetic engineering.

H.J. Mersmann: The area of genetic engineering is projected to make great contributions to plant and insect biology. In my opinion, I am not sure what the contribution of genetic engineering will be to the animal industry. One might project that if we made *in vitro* growth hormone, then we could administer this *in vitro* manufactured growth hormone to cows and increase milk production. Whether or not it is economical is not known, but this is a potential pragmatic achievable goal. If we look at animal production and think in terms of administering growth hormone to animals, assuming that growth hormone has something to do with growth in animals, we would have to administer this proteinaceous material over a relatively long period of time. Consequently, I see much less use. There may be immunological uses as has recently been done with foot and mouth disease. If you are going to genetic engineer an animal, you have to do it at the zygote level, certainly no later than the morulla stage. I don't think we understand the genetic control of adipose tissue and muscle sufficiently well to begin to talk about that.

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